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Toxicological effects of *Mentha x piperita* (Peppermint): A review

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Abstract

Peppermint (*Mentha x piperita* L.) is a medicinal plant with significant pharmacological and therapeutic activities but side effects and detrimental impacts on health have been described. Herein, we studied the literature concerning the reported inherent toxicity of peppermint. Accordingly, we classified peppermint and its main constituents in acute, subacute, chronic, developmental toxicity and cytotoxicity studies. The review outcome revealed that peppermint and its main constituents (pulegone, menthone, menthol and menthofuran) exhibit some evidence of moderate toxicity. Peppermint and its menthol isomers possess no major innate mutagenic, genotoxic or embryotoxic properties. However, there is evidence that peppermint essential oil interacts appreciably with cytochrome P450 isoenzymes to reduce or prevent their activities in rat and human liver microsomes and this has a substantial clinical implication for drug metabolism. Moreover, peppermint essential oil is contraindicated in patients with bile duct obstruction, gall bladder inflammation and liver disorders. In patients with gastrointestinal reflux or hiatus hernia, its use should be exercised with caution because it may exacerbate the symptoms of gastrointestinal reflux.

Keywords: Peppermint, Menthol, Pulegone, menthofuran, Menthone, Toxicity.

1. Introduction

Medicinal plants and herbal medicines have always played an important role in preventing and treating diseases throughout the world.[1,2] Many medicinal plants have remedial effects but are not always safe and may be capable of causing toxicity.[3,4] Based on the data from European and Brazilian poison centers gathered between 2006 and 2010, *Mentha x piperita* was reported as one of the ten most frequently used plant foods that caused adverse effects.[5]

M. x piperita L. is an ancient herbal medicine [6,7]which is a natural interspecific hybrid of spearmint (*M. spicata* L.) and water mint (*M. aquatica* L.).[8-11] The common name for *M. x piperita* is Peppermint. It is also commonly known as Nana, Brandy mint, Candy mint, Lamb mint or Balm mint all over the world.[7,9] Peppermint is a perennial, glabrous, strongly scented herb belonging to the *Lamiaceae* family.[12] Plants of this family are often used in traditional medicine for phytotherapy.[13,14]

Peppermint is a fast spreading, herbaceous rhizomatous, winter hard plant with square cross sectional smooth stems which usually grow to a height of 30–90 cm. The rhizomes are widespread and fleshy with fibrous roots.[9] The leaves are the most important part of the plant from which oil is extracted.[7] They are 4–9 cm in length and 1.5–4 cm broad being dark green in color with reddish veins, having an oblong-ovate shape with an acute apex and coarsely toothed margins (Figure 1). Both the leaves and stems are slightly hairy. The flowers are purple-pinkish, 6–8 mm long, with a four-lobed corolla of approximately 5 mm diameter which usually appears in the summer months. The chromosome number is variable, with 2n counts of 66, 72, 84, and 120.[9,15]

The peppermint herb is native to Mediterranean Europe, naturalized in the northern USA and Canada but currently cultivated all over the world. It grows well in moist, shaded areas, with high water holding capacity soil.[8,16]

Peppermint is used in various forms such as the essential oil and leaf extract. All the varieties have many uses, but the essential oil has the highest degree of general consumption[11,17] and its global production amounts to about 8000 tons per year .[9] The FDA banned the sale of peppermint essential oil over-the-counter as a digestive aid as early as 1990 because of unproven effectiveness and nowadays, peppermint is sold as a dietary supplement.[18]

The chemical constituents of *M. x piperita* are comprised of monoterpenoids, the main components of its essential oil. These include menthol (29-48%), menthone (20-31%), menthofuran (6-8%), pulegone, menthyl acetate (3-10%), limonene, pinene and piperitone in addition to caffecic acid, flavonoids like luteolin and menthoside, polyphenols including rosmaric acid, carotenes, tocopherols, narirutin, eriodictyol, tannins, betaine and choline.[6,7,9,15] An active component of peppermint essential oil which has also been

highlighted in many studies as a key ingredient of the plant, is menthol but it also contains other constituents such as its biosynthetic precursor pulegone and its metabolites menthone and menthofuran (Figure 1).[19-23]

Peppermint essential oil is currently used in the cosmetic, personal hygiene, food, beverage, pharmaceutical products and perfumery industries as a flavouring agent and for its fragrance properties.[9,24,25] Also, currently it is used widely as flavoring in ice cream, chewing gum, cigarettes, breath freshener, mouthwash, toothpaste, dental floss, confections, and tea.[11,16]

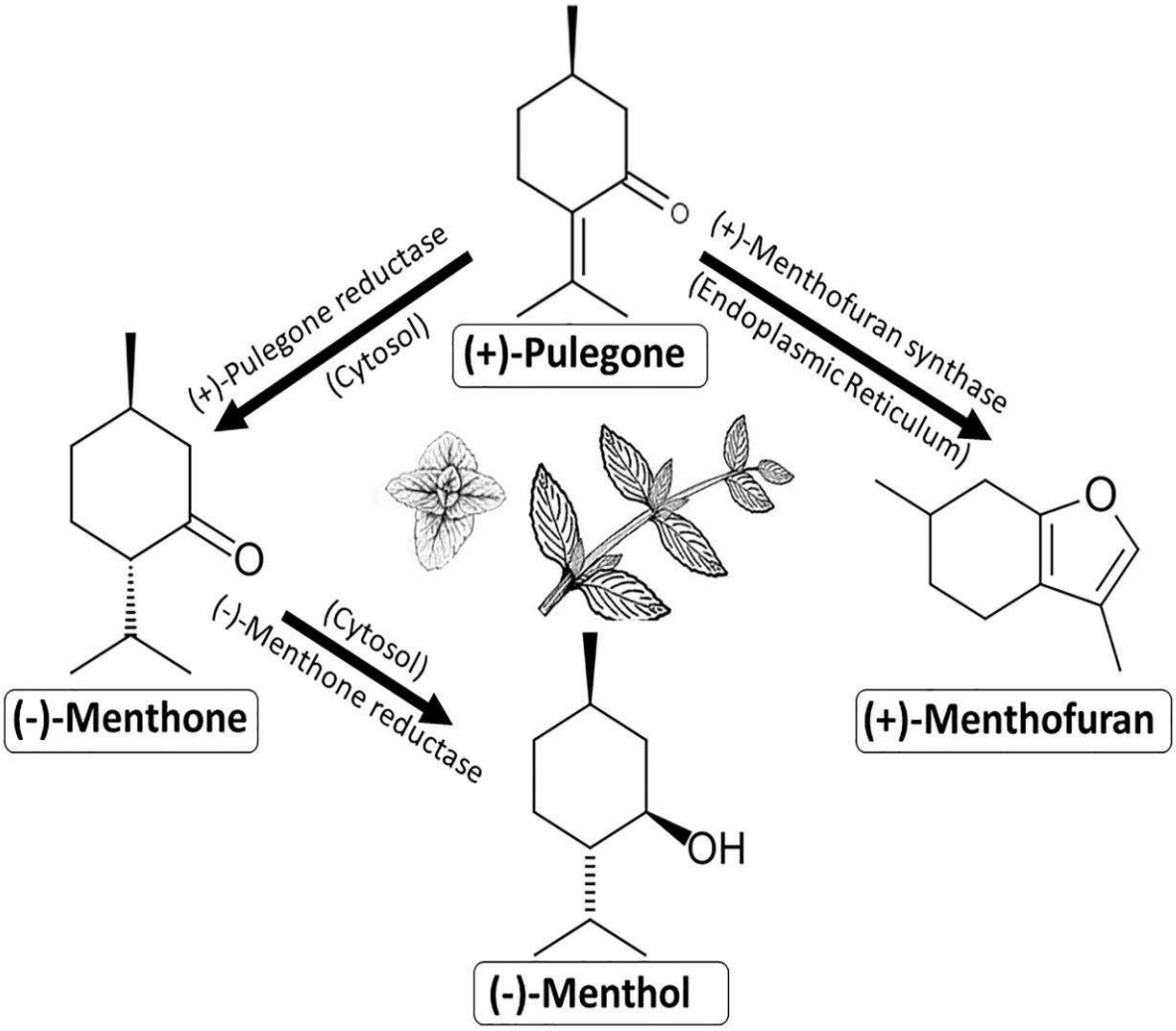

Figure 1. Biosynthetic pathway of some monoterpinoids in *M. x piperita* showing the precursor (+)-Pulegone (originally derived from (-)-Limonene) and the products (-)-Menthone, (-)-Menthol and the non-terpenoid (+)-Menthofuran[22] as the main active constituents of peppermint essential oil.[23]

Over recent years it has been demonstrated that both peppermint and its constituents induce antioxidant, antispasmodic, aromatic, antimicrobial, antibacterial, antiviral, anticarcinogenic, antitumorigenic, antiallergic, antiinflammatory, antifungal, antimutagenic, anticancer, antinauseant, antiseptic, antilipid peroxidation, antiheadache and antiobesity properties.[7,9,23,26-32]

Menthol is well absorbed by the oral route in rats (63% - 74%) and rabbits (86% - 90%).[33,34] and at ≤90%, this level is predictably much higher than that yielded by dermal absorption.[35] Subsequently, Clegg and coworkers disclosed that [^{3}H]-menthol was distributed in the urine, feces, ileum, fat, liver, serum, kidney, brain and testes.[36]

Menthol is normally metabolized in the liver to menthol glucuronide.[34,37] as the main biliary metabolite [34,37] and it is excreted in the urine and feces.[33,34,36] The other urinary metabolites consist of mono- or di-hydroxylated menthol derivatives that are eliminated as glucuronic acid conjugates.[37] In humans, menthol is excreted as the glucuronide in the urine within 12 to 24 hours after oral consumption.[38-40] (+)-Pulegone is metabolized to (-)-menthone by (+)-pulegone reductase in the cytosol and then further reduced by cytosolic (-)-menthone reductase to (-)-menthol. (+)-Menthofuran is also generated by conversion of (+)-pulegone in the endoplasmic reticulum via the enzyme (+)-menthofuran synthase (Figure 1).[22,23]

In the case of peppermint, it modulates the enzymes of phase I and phase II metabolism[41] which play an important role in biotransformation or inactivation of endogenous compounds and xenobiotics.[42] Additionally, peppermint has been shown to ameliorate the harmful effects of carbon tetrachloride on liver function.[43] Despite the widespread use of peppermint as a medicinal plant in many countries, there has been no truly comprehensive recent overall scrutiny categorizing its toxic effects *in vitro* and in animal and human studies. In view of this situation therefore, the current review was undertaken to evaluate the literature on the acute, sub-acute, and chronic toxicity of peppermint and its main products, with a focus on any possibility of induction of direct toxicity and/or developmental and mutagenic detriment.

2. Method

A comprehensive literature search was performed on scientific databases including: PubMed, Scopus, Google Scholar and Science Direct. The relevant key words used as search terms were: "*Mentha piperita*", "peppermint", "menthol", "pulegone", "menthone", "menthofuran", "chronic toxicity, sub-chronic toxicity, sub-acute toxicity, acute toxicity, mutagenicity, genotoxicity" and "developmental toxicity". Relevant full papers and abstracts were retrieved, then the reference lists of the key papers for further evaluation were searched and both *in vitro* and *in vivo* investigations were incorporated.

The toxic effects of peppermint were categorized and assigned to the following main headings of the toxicological findings: mutagenicity, genotoxicity, cytotoxicity, hepatotoxicity, carcinogenicity, embryotoxicity/developmental toxicity, carcinogenicity, clinical and preclinical toxicity.

3. Toxicological findings

A range of side effects have been reported regarding medicinal plants and natural products. These toxicological properties may occur by different mechanisms which include direct toxicity, contamination and pharmacological interactions with drugs and/or other herbs.[44]

In this particular context, the four prime potentially toxic compounds which have been identified in peppermint are menthol, pulegone, menthone and menthofuran.[9] Also, it should be noted that in the case of peppermint, the extraction method can affect the essential oil concentration. A distinctive example of this is selective ohmic-assisted hydrodistillation as compared to traditional hydrodistillation which produces variation in the chemical composition of extracted essential oils[45] and this may well influence the toxicological outcome of the extract.

3.1. *Acute toxicity*

The primary toxicity test of any chemical substance is invariably performed acutely and the median lethal dose or $LD_{50,}$ as a method of assessment, has been employed historically for many years in this regard. However, in recent years more acceptable methods of evaluation have been pursued.[46] Nonetheless, in the LD_{50} test, interspecies sensitivity, after single exposure to a chemical substance is initially observed routinely for 14 days.[47] Many factors such as animal age, weight, strain and diet influence the LD_{50} outcome value and rats and mice are the most commonly used species in the test.[47-49] Arising from LD_{50} values accumulated over time, toxicity levels of chemicals have been categorized into five different classes as follows: dangerously toxic (<1.0 mg/kg), extremely toxic (1-50 mg/kg), very toxic (50-500 mg/kg), moderately toxic (500-5000 mg/kg), slightly toxic (5000-15000 mg/kg) and practically non-toxic.[50]

LD_{50} values have been reported for peppermint essential oil at varying doses in the range 2410 – 4441 mg/kg in rats.[20,51,52] Whereas in mice, an LD_{50} >1600 mg/kg has been documented for peppermint oil[24] and at an acute dose of 0.2 ml/kg, it has not only been shown to prolong pentobarbitone-induced sleeping time but also to chronically potentiate midazolam motor incoordination.[17]

Menthol isomers (L-menthol, D-menthol and D/L-menthol) present in peppermint oil[24] have been shown to produce low acute oral toxicity with LD_{50} values typically >2000 mg/kg in rats and mice.[53] However it is noteworthy that these isomers did produce local irritancy to the eye, skin[53] and respiratory tract[54] though intraspecies studies generally

suggested there was low sensitizing activity by a variety of routes[55] (Table 1). Menthol also has insecticidal activity and in this respect, it is not only mosquitocidal[56] but it also acts as a fumigant with ovicidal activity against houseflies.[23,57]

Allergic contact dermatitis has been reported to herbal remedies using patch testing.[58] The action of L-menthol and D/L- menthol on patients with different skin conditions such as dermatoses, eczematous lesions, contact dermatitis and mucosa/skin reactions may evoke sensitivity reactions (0-6.1%). Nevertheless, the overall, sensitizing effect of menthol isomers has tended to be generally low[59-62] or even non-existent.[63]

High doses of the monoterpene ketone, pulegone, as well as menthofuran in the herb pennyroyal (*M. pulegium*), have been reported to be abortifacient.[23,64] Pulegone also possesses insecticidal toxicity against houseflies, cockroaches, rice weevils and earthworms.[65] Menthone and menthofuran, on the other hand, have both been shown to cause an increase in liver weight, hepatotoxicity and cerebellar pathology even in the short-term.[66,67] Additionally, menthofuran has been described as causing pediatric multiple organ failure[68] and as a metabolite of pulegone, it may well contribute appreciably to the overall toxicity of the parent pulegone.[69]

Table 1. Acute toxicity findings with peppermint and its main constituents.

Compound	Species	Main finding	Reference
Peppermint essential oil	Human	Overdose coma/hypoxemia, severe hypotension and shock	70
Peppermint essential oil	Mouse	LD_{50} = 1612.45 mg/kg	24
Peppermint essential oil	Rabbit	Respiratory harm	71
Menthol	Human	Coma, convulsions, hematuria, fatality	72
Menthol	Rat/Mouse	LD_{50} = 2046-2615 mg/kg	53,73
Menthol	Mouse	Respiratory tract irritation (16 ppm)	54
Menthol	Insects	Mosquitocidal	56
Menthol	Insects	House fly Fumigant/Ovicidal	23,57
Pulegone	Human	Paediatric multiple organ failure (Pulegone in pennyroyal/*M. pulegium*)	68
Pulegone	Human	Hepatotoxicity (Pulegone in pennyroyal/*M. pulegium*)	67
Pulegone	Human	Abortifacient (Pulegone in pennyroyal/*M. pulegium*)	64
Pulegone	Rat	Hepatotoxicity	74
Pulegone	Rat	≤600mg/kg Hepatotoxicity/lethality	20,75
Pulegone	Insects	House fly fumigant/ovicidal	23,57
Menthone	Rat	Hepatotoxicity and cerebellar pathology	66
Menthone	Rabbit	Intradermal Moderate/severe reactions	20
Menthofuran	Human	Hepatotoxicity (Menthofuran in pennyroal/*M. pulegium*)	67
Menthofuran	Human	Pediatric multiple organ failure (Menthofuran in Pennyroyal/*M. pulegium*)	68
Menthofuran	Human	Abortifacient (Menthofuran in pennyroyal/*M. pulegium*)	64

Peppermint essential oil, menthol, pulegone and menthone, but not menthol,[76] have been reported to create cyst-like spaces in rat cerebellar white matter.[66,77] However, later independent evaluation deduced that these pathological findings were likely to be artefacts originating from the method of tissue preparation and fixation.[78,79]

3.2. *Subacute toxicity*

Subacute toxicity is described as the effects of a specific substance that is administered at three to four different dosages to animals repeatedly over a period of 14-28 days of exposure. The results and information derived about the toxicity of a substance may then be used to determine doses for sub-chronic studies.[47,48] Thus, in this frame of reference, L-menthol has been administered in mice sub-acutely (2000-5000 mg/kg) by gavage for 5-14 days and the LD_{50} was subsequently determined as 2600 mg/kg.[53]

3.3. *Sub-chronic toxicity*

Sub-chronic toxicity tests are usually conducted in both sexes of rats, mice and dogs. Substance administration (at least three doses) is carried out for 30-90 days. The no observed adverse effect level (NOAEL), lowest observed adverse effect level (LOAEL), respiratory and cardiovascular functions, biochemical and hematological parameters, body weight, and food consumption are then recorded. The results of the sub-chronic test at that juncture are used to establish doses suitable for later chronic studies.[47,50]

Sub-chronically administered peppermint oil (100 mg/kg per day for 90 days) in rats is known to cause nephropathy (hyaline droplet formation) and cyst-like spaces scattered throughout the white matter of cerebellar tissues.[20,77] Despite this finding, there is no evidence that either encephalopathy or epithelial degeneration occurs in the brain.[80]

Analogously, B6C3F1 mice exposed to daily DL-menthol for 13 weeks exhibited a decrease in body weight and Fischer 344 rats treated for the same period displayed spontaneous interstitial nephritis (Table 2).[53] In another investigation regarding inhalational toxicity, Sherman rats were exposed to vaporized L-menthol and transient conjunctival erythema, tracheitis, pulmonary congestion, pneumonitis and severe congestion to pneumonitis, were described although exposure concentrations were not presented.[53,81]

In a study using rats, pulegone was administered by gavage at a dose of 160 mg/kg and there was a decrease in food consumption and body weight but no cerebellar pathology was observed. However, liver weight and plasma alkaline phosphatase were increased which was suggestive of an adverse hepatic effect.[82] In contrast, menthone toxicity has been described following sub-chronic treatment[75] but no adverse effects were detected when menthofuran was presented in the diet.[83]

3.4. *Chronic toxicity*

The duration of chronic toxicity testing normally involves longer than 3-months of exposure, although it tends to be extended in rodents (six months to two years) and non-rodents (one year or longer). Chronic toxicity studies are employed to evaluate the maximum tolerable dose, urinary metabolite indexes and physiological as well as pharmacokinetic aspects of the chemicals under test.[47]

There are no available reports on the chronic toxicity of peppermint in humans. However, high concentration exposure to menthol vapor has been shown not to induce chronic toxicological effects in rats.[84] Notwithstanding this, Fischer 344 rats receiving daily doses of D/L-menthol for 103 weeks, disclosed renal inflammation in the males but decreased mammary gland fibroadenomas in females[85] (Table 2). Pulegone in a two-year study however, did cause fatality in mice and rats.[86]

Table 2. Sub-chronic and chronic toxicity findings for peppermint and its main constituents

Compound	Species	Findings	Reference
Peppermint essential oil	Rat 100 mg/kg per day for 90 days	Nephropathy	80
Menthol	Human (4 days exposure)	Coma, convulsions, hematuria, fatality	72
Menthol	Human 20 years	Coma and ataxia	87
Menthol	Mouse (3913 or 4773 mg/kg/day) for 13 weeks	Body weight decrease	53
Menthol	Rat (937 and 998 mg/kg/day) for 13 weeks	Spontaneous interstitial nephritis	53
Menthol	Rat (188 or 375 mg/kg/day) for 103 weeks	Renal inflammation in males and decreased mammary gland fibroadenomas in females	85
Pulegone	Rat Oral - 28 days	NOEL <160 mg/kg/day	82
Pulegone	Rat 2-years	75mg/kg Fatality	86
Pulegone	Mouse 2-years	150 mg/kg Fatality	86
Menthone	Rat (sub-chronic)	200 mg/kg/day toxicity	75
Menthofuran	Rat (23 mg/kg) 14-day dietary	No adverse effect	83

3.5. Mutagenicity, genotoxicity, cytotoxicity, hepatotoxicity, carcinogenicity, embryotoxicity/developmental toxicity studies.

Adverse effects of medicinal plants on the development of organisms from the time of chemical or physical agent exposure at the pre-natal or post-natal stage up to the time of puberty are studied in developmental toxicity tests. Developmental toxicity includes growth retardation, structural malformations, functional or metabolic impairment and death of the organism. A component of developmental toxicity studies is reproductive toxicity which is intended to determine the adverse effects of substances on the male and female reproductive system. Correspondingly, substances that have developmental toxicity effects on the fetus are designated as teratogens.[47,49]

Data concerning the conceivable mutagenicity, genotoxicity, carcinogenicity, and developmental toxicity of peppermint and its constituents are summarized in Table 3. *In vitro*, the results of the Ames test for peppermint oil against *Escherichia coli* (WP2 uvrA) and bacterial strains of *Salmonella typhimurium* (including: G46, TA92, TA94, TA97, TA97a, TA98, TA100, TA102, TA1535, TA1537 and TA2637) did not manifest any evidence of mutagenicity.[20,88-96] Also, in the mouse lymphoma mutation test, D/L-menthol (150 µg/ml) was not mutagenic in L5178Y *tk*+/- mouse lymphoma cells.[97] Conversely however, peppermint did possess mutagenic effects in Drosophila melanogaster.[98,99]

In other studies, D/L- and L-menthol effects have been investigated in Chinese hamster ovarian cells, human peripheral lymphocytes, human embryonic lung cells and human TK6 lymphocytes. It was conspicuously clear that none of these studies revealed any significant increase in polyploidy or numbers of aberrations in any of the assays.[100-103] Moreover, the single cell comet assay on D/L-menthol cytotoxicity and genotoxicity in Chinese hamster ovary K5 cells revealed an identical absence of positive activity.[104] The possible mutagenicity of menthol in other investigations such as *Bacillus subtilis* anaphase chromosome aberration in the carcinoma prediction assay in C3H/10T1/2 cells carrying bovine papilloma virus DNA (D/L-menthol), human tissue culture cells (fibroblasts),[105] *umu DC-lacZ* genes in the *Salmonella typhimurium* strain TA1535/pSK1002,[106] also have not divulged any explicit mutagenic propensity. Conversely, the *in vitro* alkaline elution/rat hepatocyte assay which is an important test for genotoxicity, has indicated that D/L-menthol is genotoxic.[107] Furthermore, peppermint essential oil (0.30 µl/ml) generated sister chromatid exchange in human lymphocytes and induced chromosomal aberrations.[108] It also prevented cell replication and the mitotic activity of human lymphocytes. The essential oil of this herb therefore is clastogenic but it is not a typical elastic clastogen because it has a mutagenic effect on Drosophila melanogaster somatic mutation (0.20 µl/ml).[96,98,109]

Several *in vivo* studies have examined the effects of oral D/L-menthol in the comet assay in mice and all of them concluded that it was not mutagenic.[110-113] Nonetheless, in a

replicative DNA synthesis test in B6C3F1 mice and F344 rats, D/L-menthol did display mutagenic effects at a low dose after 24 hours and at a high dose after 39 hours.[111,112] Interestingly, peppermint essential oil exhibited no mutagenicity in the Salmonella/mammalian-microsome test even though menthone by itself, which is present at 33.7% in the oil, was detected as a mutagen.[88]

Antigenotoxicity effects of *M. x piperita* leaf extracts have been studied and they were found to reduce not only radiation induced chromosomal aberrations but also micronuclei in bone marrow cells from Swiss albino mice.[12,114] In addition, it was later confirmed by the same research group, that peppermint was a chemopreventive antigenotoxic agent in benzo[a]pyrene-treated animals.[115]

In early studies concerning peppermint oil carcinogenicity, mice were dosed with 4-16 mg of oil/kg/day by gavage, for 6 days per week over 80 weeks. Animal body weights were subsequently decreased but there was also evidence of concomitant lung, kidney and hepatocellular carcinoma as well as malignant lymphoma.[20,116] In overall contrast, in another contemporary investigation, peppermint essential oil was basically shown to be cytotoxic on human lymphocytes.[96] In addition, the oil has also been examined in prostate (LNCaP) and breast cancer (MCF-7) cell lines using the MTT test and a distinct potential for cytotoxicity was identified in both cell culture models.[117]

A more recent study on peppermint cytotoxicity was performed on human cancer cell lines (lung carcinoma cell line SPC-A1, leukemia cell line K562 and gastric cancer line SGC-7901) and IC_{50} values were reported as 10.89, 16.16 and 38.76 mg/ml respectively.[118] Peppermint has similarly been shown to prevent the growth of A549 non-small cell lung adenocarcinoma cells (IC_{50}=879.52 ± 22.55 μg/ml) in the MTT test and to have an inhibitory action against DNA topoisomerase I (topo I).[119] In contrast though, peppermint extract was shown to be devoid of toxicity on human (HepG2/C3A) and mouse (MH1C1) hepatoma cells. In fact, it was concluded that peppermint leaf extract was useful as a negative control.[53] Also, in B6C3F1 mice and Fischer 344 rats dosed for 103 weeks, with D/L-menthol it was concluded that it was not carcinogenic in either species.[85]

The peppermint constituent pulegone, is metabolized to piperitenone, piperitone, menthofuran, and menthone and these compounds are present in post-treatment urinary samples. As a consequence, pulegone, along with its main metabolites, were all tested for cytotoxicity in rat (MYP3) and human (1T1) urothelial cells using the MTT assay. Microscopic examination of the bladders from treated animals revealed superficial necrosis and exfoliation and there was an increased incidence of bladder neoplasms. It was deduced therefore that cytotoxicity followed by regenerative cell proliferation was at least theoretically responsible for pulegone-induced urothelial tumors in female rats .[120]

A study of peppermint on embryotoxicity during organogenesis in Balb/c mice did not reveal any evidence of a teratogenic effect even at doses up to 1200 mg/kg/day. However, fetal weights were decreased in the treatment group which was attributed either to

inhibition of cell growth via an inherent genotoxic effect or reabsorption of fetal extracellular fluid .[121]

In another study, the effect of natural Brazilian menthol was examined on a variety of pregnant species. These included mice (≤ 185 mg/kg/day on gestation days 6-15), rats (≤ 218 mg/kg on gestation days 6 to 15), hamsters (≤ 405 mg/kg/day on days 6-10 of gestation) and artificially inseminated rabbits (≤ 425 mg/kg/day on gestation days 6 to 18). The study outcome conclusion was that menthol had no teratogenic effects and that it did not incite any fetotoxic abnormalities.[20]

Although pulegone produced a negative outcome in the Ames test,[122] when given over a two-year period in mice (150 mg/kg by gavage) it yielded positive evidence of hepatoblastoma and hepatocellular carcinoma.[86] By way of contrast, menthone generated a positive in the Ames test,[123] but at a high dose, it did not produce any *in vivo* indication of a chronic pulmonary tumor response in mice.[124] More recently, menthofuran proved to be negative in the Ames test[122] and positive in the comet assay.[125]

Table 3. Mutagenicity, genotoxicity, carcinogenicity and developmental toxicity of peppermint and its constituents.

Compound	Test	Animal species or bacterium	Animal or cell culture strain	Result (+/-)	Reference
Peppermint essential oil	Ames test	*Escherichia coli*	WP2 uvrA	-	20,96
Peppermint essential oil	Ames test	*Salmonella typhimurium*	TA92, TA94, TA97 TA98, TA100, TA102, TA1535, TA1537, TA2637, G46	-	20,96
Peppermint oil **D/L-Menthol (150 µg/ml)**	Lymphoma mutation assay	Mouse	Lymphoma cells L5178Y *tk+/-*	-	97
Peppermint leaf extract	Teratogenicity test	Mouse		-	121
D/L- Menthol (1000 or 2000 mg/kg)	Replicative DNA synthesis test	Mouse	male B6C3F1 mice and F344 rats	+	111,112
D/L Menthol	Comet assay	Mouse		-	111,112
D/L Menthol	Developmental toxicity	Mouse		-	121
D/L Menthol	Developmental toxicity	Rat, Mouse and Hamster		-	20

Pulegone	Ames test	Salmonella typhimurium	TA100, TA1535 ≤10000 µg/plate	-	122
Pulegone	Carcinogenicity urinary bladder and renal damage	Rat		+	86,120,125
Pulegone	Hepatoblastoma Hepatocellular carcinoma (≤150 mg/kg gavage x 2 years)	Mouse		+	86
Menthone	Ames test	Salmonella typhimurium	TA1537	+	123
Menthone	Pulmonary tumor response	Mouse (4.75g/kg over 24 weeks)		-	75,124
Menthofuran	Ames test	Salmonella typhimurium	TA100, TA1535 ≤10000 µg/plate	-	122
Menthofuran	Comet assay	Rat		+	125

The European Medicines Agency[125] has considered whether the tumors observed in animal experiments are meaningful for human risk assessment. Substantiated in sub-chronic/chronic studies, organs of focus for pulegone as an example, are the liver and kidney.[86] Moreover, sustained cytotoxicity plus cell proliferation induced by reactive cytotoxic metabolites rather than genotoxicity appear to be underlying neoplastic mechanisms.[125] Thus, in the case of pulegone, long-term clinically non-relevant doses and continuous exposure are needed to incite neoplasms in rodents.[125] Consequently, the committee on herbal medicinal products (CHMP) has recommended a pulegone exposure limit of 0.75 mg/kg body weight per day.

3.6. Clinical studies and case reports on the side effects of peppermint and its related compounds.

In a clinical investigation performed in the 1980s subjects were exposed to 1.0 g of menthol crystal vapor for 5 minutes after which they experienced a well-documented cold sensation in the nasal passages and the familiar perception of improved airflow.[126] In addition, high doses of menthol are capable of inducing abdominal pain, convulsions, nausea, ataxia, drowsiness and coma.[127] On top of this, menthol has also been shown to cause adverse effects on the CNS (ataxia, euphoria, nystagmus and diplopia) as described in a case report on a young teenager who inhaled 200 mg of menthol.[128] On a similar note, in children younger than one year of age, intranasal administration of menthol is known to cause apnea, laryngeal and bronchial spasms and acute respiratory distress probably mediated by a reaction of the trigeminal nerve.[127,129-131]

In dermatitis tests on patients who received various concentrations of peppermint oil, there was some positive hypersensitivity.[20,61,132] In contrast, a triple-blind clinical trial on 96 pregnant women with pruritus gravidarum who took 60 ml of peppermint oil twice per day for 2 weeks displayed no adverse effects.[133] Similarly, in pediatric patients with irritable bowel syndrome who consumed 180 mg peppermint oil orally, no adverse effects were observed.[134]

Several studies have been conducted concerning the effects of different doses of peppermint in patients leading up to a variety of conditions such as: orofacial granulomatosis, lichenoid eruptions of the oral mucosa, eczema on the hands and sensitization to tixocortol pivalate, allergic contact dermatitis, allergic contact cheilitis of the lips and perioral skin, dyspnea, recurrent irritant rash and even induction of IgE mediated systemic anaphylaxis. The majority of these ailments occurred as a result of a positive allergic reaction to peppermint, often accompanied by erythema and topical sensitivity.[135-143]

Menthone administered to rats at a high dose over 28 days did display some signs of hepatotoxicity and cerebellar histopathology.[66,144] However, as mentioned previously, the

significance of this finding may warrant careful interpretation. Pulegone and menthofuran are present in the herb pennyroyal, and their effects are often extrapolated from this source. Both compounds in this respect are thought to be abortifacient[67,145,146] and menthofuran causes contact dermatitis as well as urticarial.[147,148]

3.7. Contraindications, side effects and drug interactions related to peppermint and its constituents.

Menthol administered for 28 days (≤ 800 mg/kg) in rats caused hepatocellular changes (vacuolization of hepatocytes) and pulegone (≤ 160 mg/kg) has also not only been reported to be hepatotoxic but neurotoxic as well. Consequently, it caused weight loss, atonia, decreased blood creatinine, histopathological changes in the liver and also in the white matter of the cerebellum.[149] Menthone (≤ 800 mg/kg orally) on the other hand, dose dependently decreased plasma creatinine, but increased alkaline phosphatase and bilirubin along with liver and spleen weights.[66] In a later study examining peppermint constituents for their possible induction of the encephalopathy, one-month treatment with limonene (≤1600 mg/kg) or 1,8-cineole (1000 mg/kg) produced an accumulation of protein droplets containing $\alpha_{2\mu}$ globulin in proximal tubular epithelial cells but no encephalopathy in rats.[150]

Peppermint and menthol have both been shown to possess Ca^{2+} channel blocking properties which may underlie their mechanism of efficacy against irritable bowel syndrome in the clinic.[151] However, in some patients, the use of peppermint is accompanied by oral symptoms like burning mouth syndrome and oral ulceration.[152-154] Also in this context, direct application of peppermint oil to the chest or nasal area of infants is not recommended due to the risk of apnea, bronchial and/or laryngeal spasms .[9] Peppermint essential oil also is contraindicated in patients with bile duct obstruction, gall bladder inflammation and liver disorders .[109] A further adverse effect has been detailed in rats receiving high dose peppermint tea (20g/L) where there were increased follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels but decreased total testosterone concentrations.[155]

Peppermint oil can cause heartburn or perianal irritation, bradycardia and muscle tremor, a hypersensitivity reaction, contact dermatitis, abdominal pain and jaundice in newborn babies.[7,152,156-162] (Olowe and Ransome-Kuti, 1980; Parys, 1983; Familusi and Dawodu, 1985; Nash et al., 1986; Lawson, 1988; Wilkinson and Beck, 1994; Sainio and Kanerva, 1995; Rita and Animesh, 2011; Milqvist et al., 2013). What is more, a study on a 58 year old woman who smoked menthol cigarettes also established that she suffered from gastrointestinal upsets with occasional vomiting, hand tremor, mental confusion and depression which were all ascribed to menthol.[109] (Table 4). Similarly, in another case report, a 40-year-old woman with asthma and no history of asthma or any other forms of

allergy, presented with dyspnea, wheezing and nasal symptoms after using menthol containing candies and toothpaste.[163]

There are numerous types of herbal medicine-drug interactions.[164] One of the most prevalent types of interaction occurs between herbal products and drug metabolizing enzyme systems, particularly the cytochrome P450 isoenzymes (CYP). In essence, CYP isoenzymes play a major role in the phase I metabolism of certain drugs. Peppermint oil does interact with cytochrome P450 isoforms (for example: CYP1A2/2C8/2C9/2C19/2D6 and 3A4) and therefore it may well modify the levels of drugs metabolized by those particular cytochromes.[165] A case in point is afforded by peppermint essential oil preventing cytochrome P450 izoenzyme 3A (CYP3A) activity in rat and human liver microsomes thus inhibiting cyclosporine metabolism *in vitro*.[166] Hence this type of peppermint interaction is capable of imposing a meaningful impact on drug effectiveness in the clinic.

Table 4. Case reports on the side effects of peppermint and its main constituents.

Compound	Species	Main side effect	Reference
Peppermint essential oil	Human	Vital signs disrupted ≤ 8 hours and unconscious ≤ 24 hours	70
Menthol	Human	Pain and cold hyperalgesia (at 40% concentration), ataxia and coma	72,87167,168
Menthol	Rat	Hepatocellular changes (200, 400, 800 mg) for 28 days	149
Pulegone	Human	Abortefacient, fatality (present in Pennyroyal) Serum concentration = 18 ng/ml	67,145,146
Pulegone	Rat	Weight loss, atonia, decreased blood creatinine content (Dose = 80, 160 mg) for 28 days	149
Menthone	Rat	Increased alkaline phosphatase, decreased creatinine, increased bilirubin and liver and spleen weights. NOEL = 200 mg/kg bw/day. (Dose ≤ 800 mg/kg for 28 days)	66 ,144
Menthofuran	Human	Abortefacient, fatality (present in Pennyroyal) (Serum concentration = 1-40 ng/ml)	67,145
Menthofuran	Human	Allergic contact dermatitis (erythema, vesiculation, edema). Contact urticaria. (present in Pennyroyal)	147,148

Peppermint essential oil formulated as enteric-coated capsules has been shown to be well tolerated and effective against irritable bowel syndrome.[169] Peppermint is also a risk factor for gastroesophageal reflux disease (GERD)[170] and lifestyle changes including reduced peppermint intake have been recommended by the American College of Gastroenterology.[171] In respect of this, peppermint essential oil, not only stimulates bile fluid secretion but may be involved in upregulating the bile acid synthesis-related gene, cholesterol 7α-hydroxylase (CYP7A1), and the nuclear bile acid receptor FXR (farnesoid X receptor) mRNA.[172]

It has been shown that the terpene preparation Rowachol, which contains menthol and menthone,[173] has cholelitholytic activity and its use has been recommended with careful monitoring for potential complications during cholesterol gallstone treatment.[174] A mechanism underlying Rowachol activity may derive from a combination of its cholelitholytic, choleretic and spasmolytic properties which would tend to facilitate the passage of common bile duct gallstones.[174]

4. Conclusion

Peppermint has noteworthy pharmacological effects and therapeutic uses, but side effects and drug interactions have been reported in the literature. In this review, we categorized the conceivable toxicological effects of peppermint and its main components via data bases to identify relevant scientific sources.

Various meaningful side effects of peppermint include heartburn or perianal irritation, bradycardia and muscle tremor, a hypersensitivity reaction, contact dermatitis, and abdominal pain.[154] Based on its reported LD_{50} values ($\leq$ 2000 mg/kg in rodents)[24], peppermint may be categorized as moderately toxic.

In respect of animal studies, peppermint and its component menthol isomers are devoid of any consequential mutagenicity, genotoxicity or embryotoxicity (Table 3). Be that as it may, peppermint does display carcinogenic effects such as lung and kidney cancers besides hepatocellular carcinoma at higher doses in mice. Furthermore, peppermint essential oil has a cytotoxic effect on human lymphocytes and some studies have disclosed that the oil is contraindicated in patients with, gall bladder inflammation and liver disorders.[109]

There is evidence that peppermint oil interacts appreciably with cytochrome P450 isoenzymes to reduce or prevent their activity in rat and human liver microsomes and this has a notable clinical impact on drug metabolism.[165] In view of the possibility of the toxic side effects and the potential for drug interactions with peppermint highlighted in this review, it must be a consideration that this herbal medicine is used with clinical caution.

Conflict of interests

The authors declared no competing interests.

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